pyogenes cysteine protease and a pharmaceutically acceptable carrier. Claims 6 to 17 are directed to methods of vaccinating a mammal using the claimed vaccines.

The Office Action

The title of the invention is objected to as not being descriptive. The above amendment to the title is believed to obviate this rejection.

The drawings are objected to under 37 C.F.R. § 1.84.

Claims 1-17 stand rejected under 35 U.S.C. § 101.

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bjorck *et al.*

Claims 1-17 stand rejected under 35 U.S.C. § 112, first paragraph and claims 1 and 6 stand rejected under 35 U.S.C. § 112, second paragraph.

Claims 1-4 and 6-17 stand rejected under 35 U.S.C. § 103 as unpatentable over Bjorck *et al.* Claim 5 stands rejected under 35 U.S.C. § 103 as unpatentable over Bjorck *et al.* in view of Kehoe and Fischetti *et al.*

Amendments

Applicants have amended claims 6 and 12. Support for these amendments is found, for example, at page 4 lines 14-26.

No new matter has been added by any of these amendments and the Examiner is respectfully requested to enter the amendments.

Objection to the drawings

The Applicants will submit corrected formal drawings at such time as the Examiner indicates that allowable subject matter is present.

The 35 U.S.C. § 101 Rejection

Claims 1-17 are rejected under 35 U.S.C. § 101 because the claimed invention as claimed is inoperative and therefore lacks patentable utility.

> **Applicant claims a vaccine against S. pyogenes comprising a "conserved cysteine protease". Applicants claims encompass in vivo human use. The specification fails to establish the operability of the vaccine to effect protection within the context of the claims.**
>
> **Audibert et al. (Immunology Today 14:281-284, 1993) indicates that with respect to the efficacy of "subunit" vaccines to induce protection, it is accepted now that predictions were too optimistic". Very promising immunogens have been designed, but in most cases, when tested in clinical trial, they have not induced sufficient levels of protective immunity. (see page 282, lft side)**
>
> **Thus, in general "subunit" vaccines have not proven to be effective in humans. . . .**
>
> **Applicant has provided no working examples or experimental evidence regarding the effectiveness of the claimed vaccine, peptides and fragments against the disease. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly ask for evidence to substantiate them. In re Novak, 306 F.2d 924, 134 USPA 335 (CCPA 1962), In re Fouche, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971)**

In response to this rejection, the Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 that presents evidence demonstrating the utility of the claimed invention. The experiments described in the Declaration demonstrate that immunization of mice with streptococcal cysteine protease confers significant protection against lethal group A streptococcal infection. The Declarant, an expert in the relevant field, also states that these results are reasonably predictive of therapeutic utility in humans (¶ 9). According to the interim Guidelines for Examination of Applications for Compliance with the Utility Requirement that were announced on December 22, 1994, "if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, they should be considered sufficient to support the credibility of the asserted utility" (p. 11). Therefore, the Applicants respectfully submit that this ground of rejection should be withdrawn.

The 35 U.S.C. § 112, First Paragraph Rejection

The specification is objected to and claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure.

> **Applicant claims a vaccine comprised of cysteine proteinase, fragments and derivatives thereof. H wever, Applicants have not disclosed to one of ordinary skill in the art how to use the vaccine, peptides, derivatives as a pharmaceutical or therapeutic agent. There is an insufficient written description of the invention with respect to the in vivo operability of the vaccine to enable one**

of ordinary skill in the art to use Applicant's invention for the reasons discussed in detail in the previous rejection made under 35 USC section 101.

Furthermore, Applicant has provided no teaching or guidance indicating what dosages are required and what way(s) the vaccine can be administered or otherwise used commercially. It would, therefore, require undue experimentation of one of ordinary skill in the art to determine how to use the claimed protein for the reasons previously discussed. See ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

As discussed above in the response to the rejection under § 101, the Applicants' Rule 132 Declaration provides evidence of the *in vivo* operability of the claimed invention. Furthermore, the Applicants' specification sets forth sufficient teaching to enable one of skill in the art to practice the claimed invention.

According to the Court of Customs and Patent Appeals, "[w]hat is necessary to satisfy the how-to-use requirement of § 112 is the disclosure of some activity coupled with knowledge as to the use of this activity." *In re Bundy*, 209 USPQ 48, 51 (CCPA 1981). The Applicants have disclosed that the streptococcal cysteine protease has activity as a vaccine against streptococcal infection. The Applicants' specification satisfies the first prong of the enablement requirement by disclosing that the streptococcal cysteine protease has activity as a vaccine against Group A streptococcal infection. Prior to the Applicants' invention, no effective vaccine existed against Group A streptococcal infection. Research had focused almost entirely on developing a vaccine based on streptococcal M proteins. However, as discussed in the Applicants' specification at pp. 3-4, bridging paragraph, M proteins proved ineffective for two major reasons. First, the many distinctive M protein serotypic variants requires a very heterogeneous vaccine composition. Second, the cross-reactivity of anti-M protein antibodies with heart and other human tissue may cause disease in humans. Applicants discovered that cysteine protease could be used as a vaccine instead of the M protein used in the previously known vaccination methods. Thus the Applicants have taught one skilled in the art how to make the claimed invention.

The Applicants' specification also satisfies the second prong of the enablement requirement as stated in *Bundy* by setting forth sufficient teaching to enable one of skill in the art to use the claimed vaccine discovered by the Applicants. For example, the Applicants' specification provides examples of immunization methods and dosages: examples

22 and 24, respectively, describe intranasal and subcutaneous immunization of mice. The Applicants also describe a method for measuring whether immunization with the cysteine protease has produced the desired immune response (Example 15, pages 28-29).

At the time the Applicants filed the instant application, clinicians already had significant experience in using a different streptococcal peptide, the M protein, to induce immune responses in humans. See Kehoe, *Vaccine*, pp. 797-806, 1991, for review. As explained in the attached Declaration of Dr. James M. Musser, the knowledge gained from experience with the M protein vaccines, coupled with the teachings of the Applicants' specification, enables one of skill in the art to determine appropriate dosages and formulations for the cysteine protease vaccines. For example, in Paragraphs 10 and 11, Dr. Musser describes how experiments in Beachey *et al.*, *J. Exp. Med.* 150: 862-877, 1979) provide guidance in determining an appropriate dosage regime and adjuvant. Similarly, D'Alessandri *et al.* (*J. Infect. Dis.* 138: 712-718, 1978) and Polly *et al.* (*J. Infect. Dis.* 131: 217-224, 1975) used intranasal immunization with M proteins to induce a protective response in humans. Beachey (US Patent No. 4,454,121) also provides a description of how to use M protein peptides to vaccinate humans. A copy of each of these references is of record. See the previously filed Information Disclosure Statement).

Because the general methods of immunizing against streptococcal infection were known in the prior art, it is as though they were written out in the patent application. The Applicants are not required to repeat these methods in the specification. *In re Chilowski*, 108 USPQ 321, 324 (CCPA 1956) ("It is well settled that the disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. As was said in Webster Loom Co. v. Higgins et al., 105 US 580, 586, the applicant 'may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent and delineated in the drawings.'") The teachings in the Applicants' specification, coupled with the knowledge that

one of skill in the art would glean from the prior art, allow one to use the streptococcal cysteine protease as a vaccine in humans.

The rejection asserts that determining the proper dosages and means of administration would require undue experimentation. However, as discussed above, the prior art teaches these parameters for using as vaccines streptococcal proteins other than the cysteine protease. One of skill in the art, after examining the Applicants' specification, would know to simply substitute the cysteine protease into the protocols already known for the other proteins. Thus, little experimentation is required to practice the invention. The patentability of the Applicants' invention lies in the discovery that cysteine protease could be used as a vaccine not in the mere optimization of dosages or methods of vaccination.

The Federal Circuit has recognized that the experimentation needed to perform a dose response curve is "nothing more than routine." *Merck & Co. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1847 (Fed. Cir. 1989). Similarly, in *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988), the court reversed a district court's holding that the failure to provide specific examples of dosages rendered a patent invalid for lack of enablement. The district court had found that "a dose response study typically costs about $40,000 to $50,000 to perform and requires six to twelve months." *United States v. Telectronics*, 3 USPQ2d 1571, 1578 (D. Colo. 1987). Nevertheless, the Federal Circuit held that performing a dose response study did not require undue experimentation: "[t]he only impediments are the time and cost of a dose response study, which the district court found could be performed by . . . those skilled in the art." 8 USPQ2d at 1224.

In several additional cases, patent applications that did not set forth specific dosage information were nevertheless held to satisfy the § 112 enablement requirement for claims directed to compounds having pharmacological utility. *See, e.g., In re Bundy*, 209 USPQ 48, 51 (CCPA 1981) ("We do not consider that one of ordinary skill in the art would not know how to use these novel analogs to determine the specific dosages for the various biological purposes.") *Cross v. Iizuka*, 224 USPQ 739, 748 (Fed. Cir. 1985); *Winter v. Banno*, 212, 218 (Bd. Pat App. & Int. 1985).

In an earlier case, however, the CCPA had reached the opposite result for claims directed to methods for using a compound to treat depression. *In re Gardner*, 166 USPQ 138 (CCPA 1970). In *Gardner*, the court held that the applicants had not satisfied the § 112 enablement requirement because "[t]here is not a single specific example or embodiment by way of an illustration of how the invention is to be practiced on any kind of host." *Id.* at 141. The *Gardner* applicants also failed to set forth a test for determining dose response. *Id.* at 142. Unlike the situation in *Gardner*, the instant Applicants have provided an example of how the invention is to be practiced, and have taught a test to determine dose response (*see, e.g.*, Example 15, pages 28-29). Also unlike the *Gardner* situation, the prior art contains detailed teachings of how to use as a human vaccine a peptide that is derived from the same organism as the Applicants' claimed peptide.

Furthermore, the courts have recognized that, for important new disease therapies, the public interest is best served by early filing of patent applications, rather than by waiting until clinical studies have been performed. "Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public." *In re Bundy*, 209 USPQ at 52.

The need for an effective vaccine against *S. pyogenes* is acute, in developed countries as well as in developing countries. Over six million children were estimated to suffer from rheumatic heart disease in India alone in 1981 (Agarwal, *Lancet* 1:910-911, 1981). In the United States, *S. pyogenes* causes about 25-35 million cases of pharyngitis per year, with a cost of about 1-2 billion dollars per year in direct health care costs. Although penicillin and improved living conditions have reduced the incidence of serious streptococcal diseases in developed countries, there is reason to fear that this respite may be only temporary. Kehoe states that past experience with other bacterial path gens:

> "suggests that it may only be a matter of time before we are faced with the problem f penicillin-resistant strains. We should take advantage of this time to determine if the remaining obstacles to designing an effective vaccine can be

overcome. If feasible, an effective vaccine would have immediate applications in many developing countries and could well be required in developed countries in the future." (Kehoe, *supra.* at 797-798).

The Applicants have developed an effective vaccine. However, whether this vaccine is commercially developed and thus becomes available to the public depends upon the Applicants obtaining patent protection. Requiring detailed dose response studies to satisfy the § 112 enablement requirement would place the Applicants in the "catch-22" situation of having to perform clinical studies to obtain a patent, but not being able to obtain the funding to carry out the studies because the invention is not patented. It is to correct precisely this situation that the PTO has recently announced new guidelines for assessing the utility of biotechnology inventions.

The 35 U.S.C. § 112, Second Paragraph Rejection

Claims 1 and 6 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite because there is no antecedent basis for "said mammal", as there is no first recitation of this term in the claim. Claim 6 depends from claim 1, which is accordingly rejected.

The Applicants have amended claim 6 to obviate this rejection by providing a proper antecedent basis for the term "mammal." As amended, claim 6 refers to "a mammal." Claim 12 is amended in the same manner because, although not specifically rejected, this ground of rejection could have also applied to the original claim 12.

The Applicants respectfully submit that the rejection of claim 1 on this ground is improper. Claim 1 is an independent claim and, as such, stands alone. The lack of antecedent basis in a claim that is dependent upon claim 1 is thus irrelevant to the patentability of claim 1.

The 35 U.S.C. § 102(b) Rejections

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as bvious over Bjorck et al.

The claims are directed to a vaccine comprised f cysteine proteinase, fragments or derivatives thereof.

Bjorck et al. (Nature 337:385-386, 1989) disclose a vaccine comprised of a cysteine proteinase used to "vaccinate" mice. The vaccine inhibited the growth of group A streptococcus. (see page 385, Abstract and rt side).

The prior art vaccine appears to be the same as that claimed because it is a "vaccine" comprised of a cysteine protease synthetic peptide.

The legal standard for anticipation is strict. "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991) (emphasis added). This test is not satisfied by the cited reference. The peptide described by Bjorck *et al.* has nothing in common with that utilized in the Applicants' claimed vaccines and immunization methods.

Bjorck *et al.* describe the use of an inhibitor of cysteine proteases to slow growth of group A streptococci. This inhibitor binds to the active site of the bacterial cysteine protease and prevents the enzyme from carrying out its usual reaction. This tripeptide derivative (Z-LVG-CHN_2) is not found in the amino acid sequence of the cysteine protease that is utilized in the Applicants' claimed vaccines and methods. Therefore, the Applicants respectfully submit that the Bjorck *et al.* reference does not anticipate the Applicants' invention.

The 35 U.S.C. § 103 Rejections

In the alternative, claims 1-4 stand rejected under 35 U.S.C. § 103 as obvious over Bjorck *et al.*

And if the prior art vaccine is not the same as that claimed, it is an obvious variation of that claimed, which the teachings of the prior art reference(s) would have reasonably suggested to one of ordinary skill in the art at the time the invention was made, the use of a cysteine proteinase, making the claimed invention as a whole prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made. Since the Patent Office does not have the facilities for examining and comparing Applicants' vaccine with the vaccine of the prior art (i.e., that the protein of the prior art does not posses the same material structural and functional characteristics of the claimed protein) See In re Best, 195 USPQ 430, 433 (CCPA 1977).

A necessary prerequisite for this type of "inherency" rejection is that the compounds of the invention be identical or substantially identical to that of the prior art. *In re Best*, 195 USPQ at 433 ("Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the

PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." (emphasis added))

Here, the compound described by Bjorck *et al.* has absolutely nothing in common with the compounds used in the Applicants' claimed vaccines and methods. As discussed above, the Bjorck *et al.* compound is a tripeptide inhibitor of cysteine proteases, not a derivative of a cysteine protease. The Bjorck *et al.* compound shares no part of its amino acid sequence with the compounds utilized in the claimed vaccines and methods. Therefore, the Applicants respectfully submit that *prima facie* obviousness is not established.

Claims 1-4, 6-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Bjorck et al. Bjorck et al. teach a vaccine comprised of cysteine proteinase is effective to inhibit the growth of group A streptococcus. The peptide was active in vivo.

Bjorck et al. further teach that "a cysteine proteinase is produced by all group A streptococcal strains." Bjorck et al. teach that suggest that the strategy of blocking proteinase with peptide derivatives could be useful in the construction of new agents against other microorganism, including viruses.

The prior art differs from that claimed in not using the vaccine in humans. However, as humans are also included in the host range of group A Streptococcus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to also target humans, with the expectation of similarly inhibiting the growth of group A streptococcus as demonstrated by Bjorck et al in the murine experimental model.

Again, this ground of rejection is based on a mischaracterization of the Bjorck *et al.* "vaccine." The Bjorck *et al.* "vaccine" is not comprised of cysteine protease; it is comprised of an inhibitor of cysteine proteases. In fact, it has no part of its amino acid sequence in common with the streptococcal cysteine protease. In contrast, the Applicants' claimed vaccines and methods use the cysteine protease itself, or peptide fragments based on the cysteine protease.

Nor does Bjorck *et al.* suggest that peptide derivatives of cysteine proteases could be useful in the construction of new agents against other microorganisms. What Bjorck *et al.* actually suggest is that "[t]his strategy of blocking proteinases with peptide derivatives that mimic naturally occurring inhibitors could be useful in the construction of new agents against other microorganisms . . . ." (see the Abstract)(emphasis added). These inhibitors are not peptide derivatives of cysteine protease.

Furthermore, the Bjorck *et al.* paper does not describe a "vaccine." A "vaccine" is defined as "any preparation introduced into the body to prevent a disease by stimulating antibodies against it" (Random House Webster's College Dictionary, p. 1471). The Bjorck *et al.* peptide inhibits growth of microorganisms by binding to the cysteine protease active site and preventing it from catalyzing its normal reaction. No antibody stimulation is involved. Unlike the Applicant's invention, which stimulates an immune response, the Bjorck et al. inhibitor is effective only so long as the inhibitor peptide remains in the bloodstream. Once the peptide is cleared from the body, protection is lost. The Applicant's invention, being a vaccine, confers protection against streptococcal challenge indefinitely.

Therefore, Bjorck *et al.* would not have suggested to one of skill that the cysteine protease itself is useful as a vaccine.

Claim 5 is rejected under 35 U.S.C. § 103 as being unpatentable over Bjorck et al. as applied to claims 1-4, 6- above, and further in view of Kehoe and Fischetti et al.

Bjorck et al., cited, does not add a M protein to the vaccine.

However, Kehoe (Vaccine 797-806, 1991) teach that the M proteins appear to be the only streptococcal antigens which are capable of evoking effective protection against group A infections. (see page 780)

Fischetti et al (Science 244:1487-1490, 1989) similarly teach that "type specific antibodies to the M molecule are necessary to protect [a] host once streptococcus [infection] has initiated. (see page 1490)

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to supplement the cysteine proteinase vaccine a known protective antigen, i.e., with "a M protein", as M protein antibodies appear to be the only streptococcal antigens today which are known to induce the immune response necessary to protect the host against group A streptococcal infections.

The Applicants respectfully submit that this ground of rejection is improper because the combination of references do not suggest the Applicants' invention. This claim is directed to a vaccine that comprises a streptococcal cysteine protease in combination with a streptococcal M protein antigen. As discussed above, Bjorck *et al.* does not suggest the use of a streptococcal cysteine protease as a vaccine. The secondary references likewise do not provide this suggestion.

That the Applicants' invention is not obvious is highlighted by the Examiner's statement, which was accurate prior to the Applicants' invention, that "M protein antibodies

appear to be the only streptococcal antigens today which induce the immune response necessary to protect the host against group A streptococcal infections." The Applicants have demonstrated that the streptococcal protease is even better suited to inducing an immune response, and conferring protection, than the M proteins. Thus, the Applicants respectfully request that the obviousness rejections be withdrawn.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (415) 926-6202.

Respectfully submitted,

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Dated: February 6, 1995

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